UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte IRA PASTAN, ULRICH BRINKMANN,
GEORGE VASMATZIS, and BYUNGKOOK LEE

Appeal 2007-4421
Application 09/763,393
Technology Center 1600

Decided: December 20, 2007

Before DEMETRA J. MILLS, LORA M. GREEN, and NANCY J. LINCK, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the Examiner's final rejection of claims 1, 2, 4, 6-8, 14, 15, 17, 18, and 53-57.[1] We have jurisdiction under 35 U.S.C. § 6(b). Claims 1, 2, and 17 are representative of the claims on appeal, and read as follows:

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[1] Claims 9-12, 16, 19-52, and 58-60 stand withdrawn from consideration (Br. 2).

1. An isolated polypeptide comprising
(a) an amino acid sequence set forth as SEQ ID NO: 1; or
(b) 8 to 11 contiguous amino acids of SEQ ID NO: 1, wherein the polypeptide binds major histocompatibility complex (MHC) I.

2. An immunogenic composition comprising the isolated polypeptide of claim 53, and a pharmaceutically acceptable carrier.

17. A method for inhibiting the growth of a malignant cell expressing SEQ ID NO: 1 in a mammal with a malignancy, the method comprising administering to the mammal a therapeutically effective amount of the immunogenic composition of claim 2, thereby inhibiting the growth of the malignant cell.

We affirm-in-part.

BACKGROUND

The Specification teaches:

> Here we describe the identification of an X-linked gene that is expressed in normal and malignant male and female reproductive tissues. This gene, PAGE-4 [SEQ ID. NO: 1] (which we originally called PAGE-1 and have now renumbered to be consistent with other findings), is homologous to a family of MAGE/GAGE like proteins and is expressed in normal prostate, testis, uterus, fallopian tube and placenta, as well as in prostate, testicular and uterine cancers.

(Specification 5).

The Specification teaches further:

> The specific detection of PAGE-4 is expected to be valuable for the diagnosis of prostate and testicular tumors, as well as uterine tumors. There are sufficient differences between PAGE-4 and other members of the PAGE and MAGE antibodies to produce specific antibodies, and we have demonstrated the production of PAGE-4 antibodies. Analyses

> with such antibodies is expected to confirm by immunohistology the expression specificity that is seen in database and mRNA analyses. The antibodies can also be used to detect the presence of PAGE-4 in biological samples. In *in vitro* applications, the antibodies can be used in any of a number of standard immunoassays. For example, the sample can be contacted with mouse anti-PAGE-4 antibody, washed with buffer, and tested for the presence of bound antibody using a goat anti-mouse antibody (antisera from a goat which recognizes mouse antigens). Alternatively, the presence of PAGE-4 can be determined by detecting the presence of mRNA encoding PAGE-4, through PCR or any of several other assays known in the art.
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> Since removal of normal prostate, testis or uterine tissue, together with the cancerous lesions, is part of standard cancer therapy, the detection of PAGE-4 in body tissues following removal of the lesions and of the organs expected to express PAGE-4 indicates that not all of the cancerous tissue has been removed. Accordingly, detection of PAGE-4 protein can be a valuable signal that further steps may be needed to eliminate the cancer.

(*Id.* at 18-19)

The PAGE-4 gene was identified using database mining, through a computer screening strategy to identify genes that are preferentially expressed in normal prostate and in prostate cancer (*id.* at 12). According to the Specification, "all or part of the PAGE-4 gene product can be used as a vaccine to enhance the immune system's ability to eliminate PAGE-4 containing cells." (*Id.* at 17.) The Specification discusses strategies for the generation of such vaccines, such as identification of potential CTL epitopes (*id.* at 20-23). The Specification, however, does not provide any working examples of identifying such peptides from the PAGE-4 polypeptide of SEQ

ID NO:1 and confirming that the peptide is in fact a CTL epitope or that its binds major histocompatibility complex I.

DISCUSSION

Claims 1, 2, 4, 6-8, 14, 15, 17, 18, and 53-57 stand rejected under 35 U.S.C. § 101 "because the claimed invention is not supported by either a specific asserted utility or a well established utility." (Answer 6.)

The Examiner bears the initial burden of showing that a claimed invention lacks patentable utility. *See In re Brana*, 51 F.3d 1560, 1566 (Fed. Cir. 1995). ("Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility.").

The Court of Appeals for the Federal Circuit addressed the utility requirement in *In re Fisher*, 421 F.3d 1365 (Fed. Cir. 2005). The *Fisher* court interpreted *Brenner v. Manson*, 383 U.S. 519 (1966), as rejecting a "de minimis view of utility." 421 F.3d at 1370. The *Fisher* court held that § 101 requires a utility that is both substantial and specific. *Id.* at 1371. The court held that disclosing a substantial utility means "show[ing] that an invention is useful to the public as disclosed in its current form, not that it may prove useful at some future date after further research. Simply put, to satisfy the 'substantial' utility requirement, an asserted use must show that that claimed invention has a significant and presently available benefit to the public." *Id.*

The court held that a specific utility is "a use which is not so vague as to be meaningless." *Id.* In other words, "in addition to providing a

'substantial' utility, an asserted use must show that that the claimed invention can be used to provide a well-defined and particular benefit to the public." *Id.*

With respect to diagnosis, the Examiner argues, citing numerous references such as Yokata,[2] that one "cannot determine that SEQ ID NO: 1 or its fragment could be used successfully for *diagnosis* of cancers that express SEQ ID NO: 1, because, although the polynucleotide encoding SEQ ID NO: 1 is differentially expressed in prostate and uterine cancers as compared to normal controls, one cannot predict that the encoded SEQ ID NO: 1 is also *differentially* expressed in prostate and uterine cancers as compared to normal controls, in view that protein levels cannot be predictably correlated with steady-state mRNA levels or alterations in mRNA levels." (Answer 7.)

The Examiner has not established that one of skill in the art would find the Specifications of the utility of the claimed polypeptide and fragments thereof to be incredible. As noted by the Examiner in the rejection, the polynucleotide encoding SEQ ID NO: 1 is differentially expressed in prostate and uterine cancers as compared to normal controls. Thus, the skilled artisan would have understood that the claimed polypeptide of SEQ ID NO:1 would have utility as a cancer marker, as well as utility in

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[2] Yokata et al., "Altered expression of the retinoblastoma (RB) gene in small-cell carcinoma of the lung," *Oncogene*, Vol. 3, pp. 471-475 (1988). The Examiner cites Yokata for its teaching that "the retinoblasma (RB) 115 kD protein is not detected in all nine cases of lung small-cell carcinoma, with either normal or abnormal size mRNA, whereas the RB protein is detected in three of four adenocarcinomas and all three squamous cell carcinomas and one of two large cell carcinomas expressing normal size RE3 mRNA." (Answer 8.)

generating antibodies specific to the polypeptide of SEQ ID NO: 1. Thus, the claimed polypeptide has a significant and presently available benefit to the public.

We have considered the Examiner's assertions that protein levels cannot be predictably correlated with steady-state mRNA levels. As discussed by the Pastan Declaration[3] (¶ 9), however, there is a strong correlation between mRNA levels and protein expression for the PAGE4 polypeptide of SEQ ID NO: 1, and the Examiner has not presented any evidence specific to that polypeptide to refute the evidence provided by the Declaration.

The Examiner argues further that "[t]he specification discloses that the peptide of SEQ ID NO: 16 could be used for generating antibodies. However, there is no indication that the antibody is specific for SEQ ID NO: 1, in view of the disclosed similarity of SEQ ID NO: 1 and known polypeptides, such as MAGE, GAGE or other PAGE polypeptide." (Answer 7.)

The generation of antibodies specific for a particular polypeptide is well established and well known in the art. *See In re Wands*, 858 F.2d 731, 736 (1988). The Examiner has not provided evidence that the skilled artisan would have found the generation of antibodies specific to SEQ ID NO: 1 using either the entire polypeptide of SEQ ID NO: 1 or the claimed fragments of the polypeptide as the antigen to be incredible, such as to support a conclusion that the claimed polypeptide of SEQ ID NO: 1 and the peptide fragments thereof would lack a patentable utility.

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[3] All references to the Pastan Declaration are to the Declaration of Dr. Pastan, first submitted March 13, 2006, also attached to the Appeal Brief.

As to the therapeutic applications, the Examiner asserts that "one cannot determine that SEQ ID NO: 1 or its fragments that bind to MHC, including the CTL peptide, amino acids 16-25 of SEQ ID NO: 1 could be used successfully for *cancer treatment*, because cancer immunotherapy is unpredictable. Further experimentation is required to determine what the use is for the claimed polypeptides of SEQ ID NO: 1 or its fragments of 8 to 10 or 11 amino acids that binds MHC I." (Answer 9.)

The Examiner cites Kirkin[4] as teaching "that although several CTL peptides have been tested in vivo, so far only two patients [have a] response to these peptide antigens in vivo, and that in particular, for CTL peptides of the MAGE families, *only one* peptide, EVDPIGHLY of MAGE-A3, has limited *anti-tumor* activity, indicating their low immunogenicity." (Answer 9.)

That teaching of Kirkin cited by the Examiner, however, in fact supports a finding that the claimed polypeptide and fragments thereof, as well as the treatment methods, do not have an incredible utility. We do not find "that the nature of applicants' invention alone would cause one of skill in the art to reasonably doubt the asserted usefulness." *Brana*, 51 F.3d at 1566. Kirkin demonstrates usefulness of the claimed polypeptide by the fact that one peptide had limited tumor activity that the claimed therapeutic methods do "not suggest an inherently unbelievable undertaking or involve implausible scientific principles." (*Id.*)

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[4] Kirkin et al., "Melanoma-associated antigens recognized by cytotoxic T lymphocytes," *APMIS*, Vol. 106, pp. 665-679 (1998).

The Examiner also cites several other references, notable among which is Spitler.[5] Spitler is cited for recognizing the unpredictability of the art, stating: "Ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: 'cancer vaccines don't work'. Ask a venture capitalist or the director of product development at a large pharmaceutical company and you're likely to get the same response." (Answer 10 (quoting Spitler, p. 1).)

Spitler goes on to state, however, that "[c]ancer vaccines have been used clinically since the turn of the century and continue to be widely used in cancer therapy." (Spitler, p. 1.) Thus, Spitler also provides evidence that the claimed therapeutic methods are not an inherently unbelievable undertaking or involve implausible scientific principles. We do note, however, that the Examiner's arguments would have been more appropriate in a rejection under 35 U.S.C. § 112, first paragraph, on the grounds that the Specification fails to enable the claimed therapeutic methods.

Thus, we agree with Appellants that the Examiner has not provided a sufficient basis to challenge the Specification's assertion of utility, and the rejection is reversed.

Claims 1, 2, 4, 6-8, 14, 15, 17, 18, and 53-57 stand rejected under 35 U.S.C. § 112, first paragraph, on the grounds that "since the claimed invention is not supported by either a specific asserted utility or a well established utility . . ., one skilled in the art clearly would not know how to use the claimed invention." (Answer 13.)

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[5] Spitler, "Cancer Vaccines: The Interferon Analogy," *Cancer Biotherapy*, Vol. 10, pp. 1-3 (1995).

To the extent that the rejection is based solely on the lack of utility, this rejection is reversed.

Claims 14, 15, 17, and 18 stand rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the Specification would not have enabled one skilled in the art to make and/or use the claimed invention.

Enablement is a question of law, based on underlying findings of fact. *See, e.g., Wands*, 858 F.2d at 735. "When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application." *In re Wright*, 999 F.2d 1557, 1561-62 (Fed. Cir. 1993).

"[T]o be enabling, the specification . . . must teach those skilled in the art how to make and use *the full scope of the claimed invention* without 'undue experimentation.'" *Wright*, 999 F.2d at 1561 (emphasis added), *quoted in Genentech, Inc. v. Novo Nordisk, A/S,* 108 F.3d 1361, 1365 (Fed. Cir. 1997). Thus, "there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed." *In re Vaeck*, 947 F.2d 488, 496 & n. 23 (Fed. Cir. 1991), *quoted in Enzo Biochem, Inc. v. Calgene, Inc.,* 188 F.3d 1362, 1372 (Fed. Cir. 1999).

"Patent protection is granted in return for an enabling disclosure . . . , not for vague intimations of general ideas that may or may not be workable." *Genentech*, 108 F.3d at 1365. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim

certainly need not have been carried out by an inventor, or exemplified in the specification, *reasonable detail* must be provided in order to enable members of the public [skilled in the art] to understand and carry out the invention." *Id.* at 1366 (emphasis added).

With respect to the *Wands* factors the Examiner focuses on the lack of guidance in the Specification, the unpredictability of the art and the lack of working examples. The Examiner relied on Kirkin for teaching that "although the specific peptide 27-35 of Melan-A/MART-1 induce CTL response in vitro, other Melan-A/MART-1 peptides having *higher affinity* to the HLA-A2.1 do not induce the generation of melanoma-specific CTL." (Answer 13.) As to the Pastan Declaration, the Examiner notes "other than the CTL peptide 16, or amino acids 16-25 of SEQ ID NO: 1, as disclosed in the Declaration by Dr. Pastan, one cannot predict *which* other peptides of SEQ ID NO: 1 that bind to MHC I could be used for the claimed method of cancer treatment, because not any peptides that bind to MHC have the ability to induce CTL lysis of target cells, a property necessary for their potential use in cancer treatment." (*Id.*) The Examiner thus concludes that "it would be undue experimentation for one of skill in the art to practice the claimed invention as broadly as claimed." (*Id.*)

In response, Appellants specifically address each of the *Wands* factors (Br. 29-31). We focus on the ones which we find to be determinative on the issue of whether the Specification would have enabled one skilled in the art to practice the subject matter of claims 14, 15, 17, and 18.

As to the state of the art and the predictability of the art, Appellants argue that the "use of immunogenic peptides to inhibit the growth of a malignant cell is well known in the art. The state of the art is evidenced by

Visseren et al.[6], who describes the use of MAGE proteins for the treatment of melanoma." (*Id.* at 29.) Moreover, Appellants assert, "Once the sequence of an immunogenic peptide is determined, the use of that peptide to induce an immune response against a cell expressing SEQ ID NO: 1 is predictable. Once the amino acid sequence of a polypeptide is known, that polypeptide can be used to produce activated T cells . . . that can lyse tumor cells expressing the full-length polypeptide." (*Id.* at 30.)

Visseren identified 7 MAGE-2 derived peptides that bind "with sufficient affinity" to HLA-A*0201 (Visseren, p. 125, second column). Three of the peptides were able to form stable complexes with MHC-1 and were capable of eliciting a CTL response in HLA-A*0201K^b transgenic mice (*id.*). Two of the peptides were processed by HLA-A*0201 (*id.*). There was no recognition, however, of HLA-A*0201$^+$ melanoma cell lines, but the authors state that finding may be due to the fact that human HLA-A*0201K^b melanoma cell lines do not express the murine MHC I α3-domain, "causing less optimal conditions for recognition by murine CD8+ CTLs." (Visseren, p. 129, paragraph bridging the first and second columns.) Visseren, however, did not look at the ability of activated T-cells to lyse tumor-cells expressing the full-length polypeptide. Thus, Visserin does not support Appellants assertion that the use of immunogenic peptides to inhibit the growth of a malignant cell is well known in the art.

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[6] Visseren et al., "Identification of HLA-A-*0201-Restricted CTL epitopes Encoded by the Tumor-Specific *Mage-2* Gene Product," *Int. J. Cancer*, Vol. 73, pp. 125-130 (1997).

Kirkin, cited by the Examiner, further supports the unpredictability of the art. Kirkin teaches that a strong immune response to differentiation antigens is limited by the existence of tolerance to these "self-antigen." (Kirkin, abstract.) Kirkin notes that a "large number of antigenic epitopes have been characterized in these antigens," but that preliminary results in clinical trial have not been promising (*id.* at p. 666, first column). Kirkin also discusses an immunodominant peptide from Melan-A/MART-1, wherein "the immunization of . . . melanoma patients with immunodominant peptide 27-35, increasing the frequency of Melan-A/MART-1 specific CTL, did not induce tumor regression." (Kirkin, p. 670, second column.) Thus, Kirkin is evidence that the induction of a specific CTL does not necessarily translate to the ability to induce tumor regression.

As to the amount of direction provided in the application and the existence of working examples, Appellants argue that the use of PAGE4 peptides to produce an immune response, and their use for the treatment of cancer, is provided in the Specification (Br. 30). In addition, Appellants argue, pharmaceutical formulations for immunogenic compositions are well known in the art, and are also described in the Specification (*id.*). The Specification, Appellants argue, provides SEQ ID NO: 1, and the Pastan Declaration "documents that, using the guidance provided by the specification, cytotoxic lymphocytes (CTLs) could be produced that lyse malignant cells expressing SEQ ID NO: 1." (*Id.*)

We first note that there are no working examples provided in the Specification. The Specification does discuss strategies for the identification of potential CTL epitopes, but as evidenced by Kirkin, the induction of a

specific CTL does not necessarily translate to the ability to induce tumor regression.

The only working example provided is contained within the Pastan Declaration. Dr. Pastan states that "[u]sing the information disclosed in the specification, the primary amino acid sequence of human PAGE4 was analyzed for consensus motifs for novel HLA-A2 binding peptides using a computer program." (Pastan Declaration, ¶ 4.) Three PAGE4 peptides (Pastan Declaration, Table 1) were synthesized, two of which bound to HLA-A2 molecules (Pastan Declaration, ¶ 4). The peptides were then evaluated to determine the stability of the peptide-MHC complex (*id.*).

PAGE4 specific T-cell lines (PAGE3 specific CTLs) were then generated from a prostate cancer patient using the two peptides which bound to HLA-A2 molecules (Pastan Declaration, ¶ 5). The specificity of the PAGE4 specific T cells was analyzed for their ability to release IFN-γ after stimulation with autologous B cells pulsed with the corresponding peptides (*id.*). Both cell lines produced IFN-γ, although the T-A-P16 produced it at higher levels (*id.*).

The T-A-P16 cells were then analyzed to determine if they could lyse tumor cells that endogenously express native PAGE4 (Pastan Declaration, ¶ 7). *In vitro* studies demonstrated that "T-A-P16 cells were capable of lysing LNCaP human prostate cancer cells that express native PAGE4 and are HLA-A2 positive. At an effector: target ratio of 30: 1 approximately 15% of the target cells were lysed, while at an effector:target ratio of 15:1 approximately 8% of the target cells were lysed."

The Declaration is not convincing. First, it only demonstrates that the P16 peptide is capable of inducing a CTL response that is capable of lysing

target cancer cells. The claims are not limited to the P16 peptide, but encompass methods using the entire PAGE4 polypeptide as well as any peptide comprised of 8 to 11 contiguous amino acids of the PAGE4 polypeptide. Thus, the Declaration does not provide support for the enablement of the full scope of the claimed subject matter.

Second, the Declaration demonstrates that in *in vito* studies at an effector: target ratio of 30: 1 approximately 15% of the target cells were lysed, while at an effector:target ratio of 15:1 approximately 8% of the target cells were lysed. Thus, only a small percentage of cancer cells were lysed *in vitro*. One skilled in the art would have expected those percentages to go down even more *in vivo*, such that the ability of the T-A-P16 cells to lyse tumor cells that endogenously express native PAGE4 may be negligible. The skilled artisan would have understood that the use of therapeutics *in vivo* is inherently unpredictable.

Our conclusion is not inconsistent with the Federal Circuit's decision in *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995). The court quoted *In re Krimmel*, 292 F.2d 948, 953 (CCPA 1961), which stated:

> "We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though in may eventually appear that the compound is without value in the treatment of humans."

Brana, 51 F.3d at 1567.

In the case before us, the Pastan Declaration demonstrates that only low levels of cell lysis were found *in vitro*, which, as noted above, the skilled artisan would not have expected to translate to *in vivo* levels of cell

lysis. Although speaking in terms of utility, the above quoted statement of the Federal Circuit was made in the context of review of a rejection under 35 U.S.C. 112, first paragraph, for lack of enablement. *Brana*, 51 F.3d at 1568. In contrast with *Brana*, in this case we have no data from an art-accepted model, nor any evidence that the *in vitro* results obtained in the Pastan Declaration are predictive of the results that would have been expected *in vivo* in an art-accepted model.

With respect to the quantity of experimentation, Appellants assert the claimed polypeptide of SEQ ID NO: 1, as well as its fragments, can be readily produced and screened to demonstrate that it binds MHC and can induce a T cell response (Br. 30.) Moreover, according to Appellants:

> The production of antigen specific cytotoxic T cells is routine for one of skill in the art . . . . One of skill in the art can perform these assays. The Declaration of Dr. Pastan provides further evidence that, using methods such as those described in the specification, a polypeptide consisting of nine consecutive amino acids of SEQ ID NO: 1 can be used to activate cytotoxic T cells. These T cells can lyse prostate cancer cells *in vitro.* This evidence supports the assertion that the specification is fully enabling for the use of the claimed polypeptides.

(*Id.* at 31.)

Contrary to Appellants' assertions, we find that it would have required an undue amount of experimentation to practice the methods of claims 14, 15, 17, and 18, given the state of the prior art, the unpredictability of the art, the lack of guidance provided by the Specification, and the lack of working examples. We therefore conclude that a preponderance of the evidence supports the conclusion that one skilled in the art could not have practiced the methods of claims 14, 15, 17, and 18 without an undue amount of

experimentation, and thus would not have been enabled by the Specification. *See, e.g., Ethicon, Inc. v. Quigg*, 849 F.2d 1422, 1427, 7 USPQ2d 1152, 1156 (Fed. Cir. 1988) (explaining the general evidentiary standard for proceedings before the Office).

The rejection is therefore affirmed.

CONCLUSION

In summary, we reverse the rejection of claims 1, 2, 4, 6-8, 14, 15, 17, 18, and 53-57 under 35 U.S.C. § 101. We also reverse the rejection of claims 1, 2, 4, 6-8, and 53-57, under 35 U.S.C. § 112, first paragraph, for lack of an enabling disclosure, but affirm as to claims 14, 15, 17, and 18.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED-IN-PART

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